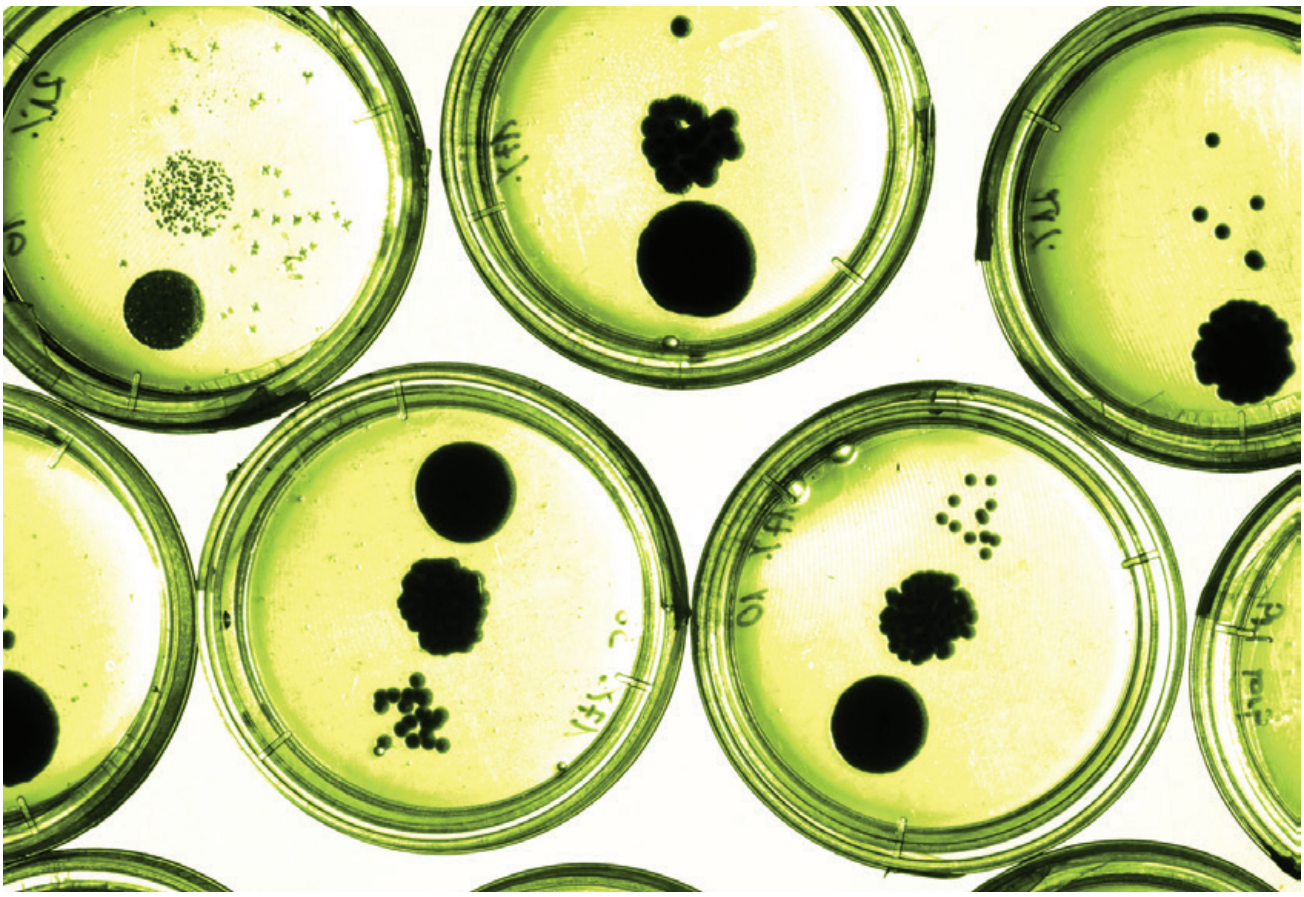

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Put to the Test

Typical Phase 1 oncology studies have changed and evolved as new techniques have developed, and target therapies have begun to reach the market. By looking at the types of drugs used, the dose levels tested and the patient populations focused on, it is possible to see where the current emphasis lies, and where unmet needs remain

Lindy Bosch and Raymond Hoffmans at SMS-oncology

Cancer is one of the leading causes of death. In 2012, there were 14.1 million new cancer cases reported and 8.2 million people died of the disease (1). Despite the passing of more than four decades since the war on cancer started with the signing of the US National Cancer Act of 1971, there is still a significant unmet medical need in this area. It is estimated that only 13% of the anti-cancer molecules currently under investigation will be approved for marketing in the US (2).

The traditional clinical development path of cytotoxic anti-cancer drugs starts with a Phase 1 dose escalation trial in which the safety and tolerability of a compound is assessed, establishing the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). If the cytotoxic drug is safe and tolerable, it will be used in a Phase 2 study at the MTD or RP2D to assess the efficacy of the drug. The efficacy will be measured by response rate, which describes the percentage of tumour shrinkage. If positive signs are shown, a randomised Phase 3 study starts, during which the cytotoxic drug is compared with the standard of care (SoC) regimen (SoC plus study drug versus SoC). The primary end-point of the randomised Phase 3 study is most often median overall survival.

Study Statistics

As more and more targeted therapies are in development and reaching the market, it is interesting to consider what a typical oncology Phase 1 study looks like nowadays. To answer this question, we performed a PUBMED search for full-length articles published in English in 2012 or 2013 that describe Phase 1 (or Phase 1/2) studies in adult patients with solid tumours, in

which single anti-cancer agents were tested. A total of 191 studies fulfilled these search criteria (3), and in total, 7,051 cancer patients were enrolled in these studies. The mean number of patients per study was 36.9 (range 4-296) and, on average, 2.3 sites (range 1-11) participated in the studies. The average enrolment time was 26.0 months, whereas the mean study duration was 31.4 months, suggesting an average of five to six months of treatment and follow-up after the last patient has been enrolled in a study (see Table 1).

Table 1: General characteristics of oncology Phase 1 studies

	Patients (#)	Sites* (#)	Study enrolment* (months)	Study duration* (months)
N (# studies)	191	130	89	34
N (# patients)	7,051	4,332	3,278	1,806
Mean (range)	36.9 (4-296)	2.3 (1-11)	26.0 (3-80)	31.4 (6-55)
Median (Q1:Q3)	26.0 (15.0:44.0)	2.0 (1.0:3.0)	23.0 (17.0:33.0)	32.5 (22.3:40.5)

*N (# studies) indicated the number of studies that are reported in the parameter

The 191 studies were performed across 24 countries. As expected, the US was the nation most often involved in these trials, with almost half (48%) of the reported studies having at least one site in the country. Surprisingly, Japan was the second country, involved in 17% of all trials, followed by the UK with 8%. Other countries participating in more than two trials were China, Canada and Australia, and in Western Europe, France, Germany, Spain and The Netherlands.

In 65.4% of the studies described, pharmaceutical companies were the sponsor of the trial. Meanwhile, academia and biotechnology companies were the sponsors in 18.3% and 17.8% of the studies, respectively.

Types of Drug

The vast majority of the 191 Phase 1 studies were conducted with small molecules (66.0%), as can be seen in Figure 1, part A. The other drug types used in these studies included large molecules (9.4%), peptides (8.9%), cell therapy (5.8%), oligo nucleotides (4.2%) and viruses (3.1%).

Although the route of administration (RoA) varied among the 191 studies (see Figure 1, part B), the vast majority of patients received their medication either orally (PO) (37.7%) or by intravenous administration (IV) (41.9%). A small percentage of studies also used a combination of PO and IV (2.6%). Other RoA included intradermal (6.8%), subcutaneous (3.7%), intramuscular (2.1%), intratumoral (2.1%), intravesical (1.6%), intrapleural (1.0%) or subconjunctival administration (0.5%).

Dose Levels

Phase 1 trials often involve a dose escalation component in order to find the MTD or RP2D that can then be used in Phase 2 studies. Around 10% of the 191 studies only tested one dose level, but the other 90% tested several. The median (Q1:Q3) number of dose level tested was five (3.0:7.5), while the maximum number tested in a single study was a staggering 23. A median dose level of five is what we would have predicted before we conducted this exercise.

In a dose escalation trial with the goal of establishing MTD, if only one to two dose levels are tested, it can be argued that the starting dose was too high and that the safety and well-being of the patient was at risk. However, if more than seven dose levels are tested, it can be said that the starting dose was too low, and that patients in the first cohorts were treated at sub-optimal doses at which no, or limited, therapeutic benefit could be expected. In both instances, this is an ethical issue. On the one hand, the doctor has to safeguard the safety and well-being of the patient; on the other, he or she wants to limit the number of patients treated at sub-optimal doses.

Patient Population

Traditionally, oncology Phase 1 trials were so-called 'all-comers" trials. In these studies, the inclusion and exclusion criteria did not specify the type of solid tumour the patient needed to have to be eligible, and thus patients with all kinds of solid tumours could be enrolled. As targeted therapy has made its entrance, this has changed. With targeted therapies, there is often a molecular or genetic reason as to why the drug will only work in certain patient populations. Therefore, we assessed how many of the 191 studies focused on a specific indication and how many allowed for multiple indications. Almost a quarter of the studies focused on a single indication

Figure 1: Type of drug and route of administration

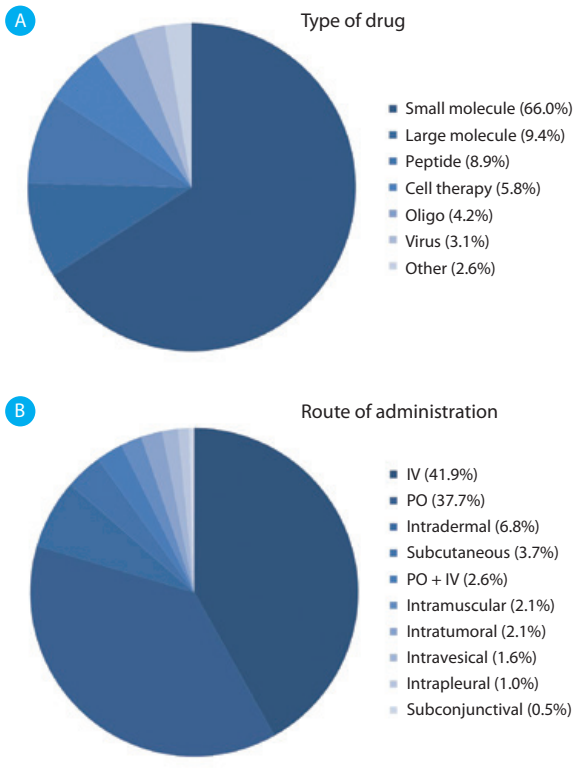
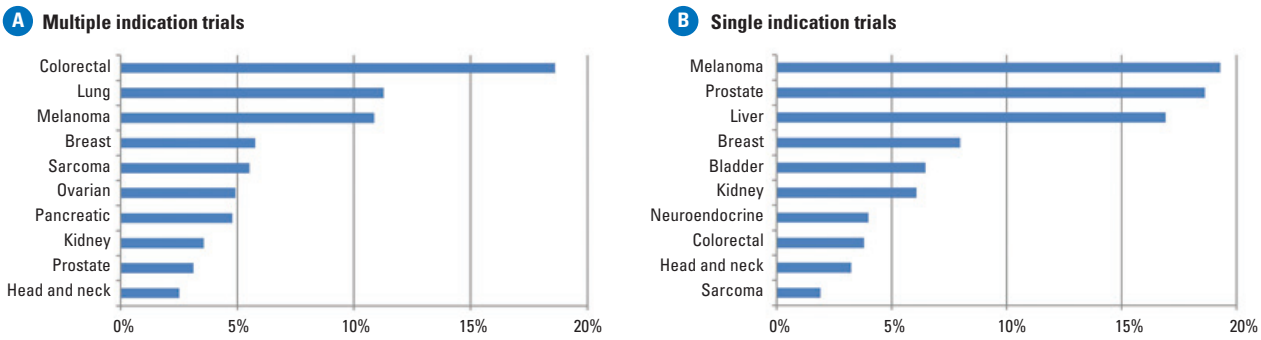


Figure 2: Patient population



(44 studies with 1,052 patients in total), compared with 147 of them which allowed for multiple ones (5,999 patients in total).

Figure 2, part A, shows the top 10 indications that are most often enrolled in trials allowing for multiple indications. Colorectal cancer, lung cancer and melanoma patients are the three groups that are most often enrolled (18.6%, 11.3% and 10.9% of patients, respectively). While the list is completed in descending order by breast cancer (5.8%), sarcoma (5.5%), ovarian cancer (4.9%), pancreatic cancer (4.8%), kidney cancer (3.6%), prostate cancer (3.1%) and head and neck cancer (2.5%). These 10 indications comprise less than 70% of the total patient population in Phase 1 trials allowing for multiple indications.

We also looked at the top 10 indications for trials that focus on a single indication (see Figure 2, part B). In descending order, these are melanoma (19.3% of patients), prostate cancer (18.6%), liver cancer (16.9%), breast cancer (8.0%), bladder cancer (6.5%), kidney cancer (6.1%), neuroendocrine cancer (4.0%), colorectal cancer (3.8%), head and neck cancer (3.2%) and sarcoma (1.9%). Interestingly, in the top 10 indications for trials with multiple indications, lung, ovarian and pancreas cancer are represented, although these are missing from the top 10 appearing in single indication trials. On the other hand, liver, bladder and neuroendocrine cancer are among the top 10 indications for trials with single indication, but are missing from the top 10 in multiple indication trials.

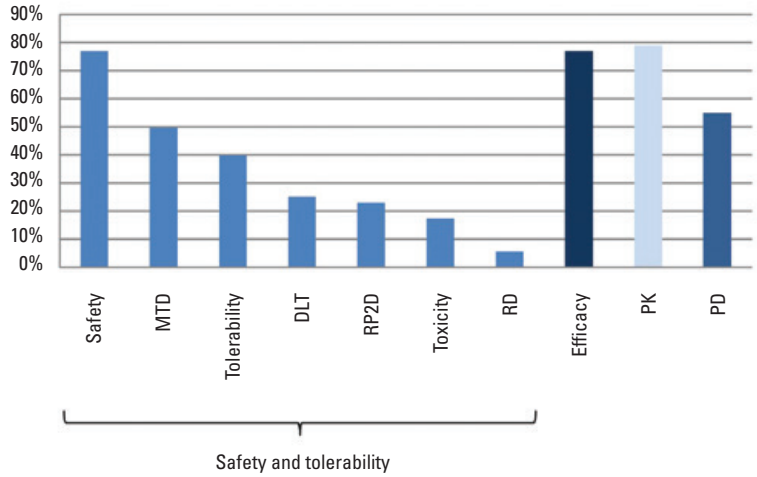
The top five cancers with the highest incidence rate worldwide are lung, breast, colorectal, prostate and stomach cancer (1). Four of these cancers are seen in the top 10 indications in the Phase 1 trials we analysed. Surprisingly, stomach cancer – which is the fifth most common cancer – is not among the top 10 indications.

Objectives

Traditionally, the objective of Phase 1 trials is to assess the safety and tolerability of an anti-cancer drug, thereby determining the MTD and/or RP2D. The most often reported objectives (primary and secondary objectives combined) in the 191 studies are pharmacokinetics (PK) (79% of the studies), efficacy (77%), safety (77%), pharmacodynamics (PD) (55%), MTD (50%), tolerability (49%), dose limiting toxicity (DLT) (25%), RP2D (29%), toxicity (17%) and recommended dose (RD) (6%). As can be seen from this list, and as displayed in Figure 3, the traditional objectives related to safety and tolerability (safety, MTD, tolerability, DLT, RP2D, toxicity and RD) are still assessed in the current Phase 1 trials. The majority of studies also look at the PK and the efficacy of the anti-cancer drug, as well as the outcomes of these two objectives, which can be correlated to create or predict dose-response relationships of the anti-cancer drug.

As more and more molecular-targeted agents enter the clinic, PD is becoming increasingly important. The goal of a biomarker is to predict the efficacy of these agents – allowing for the selection of patients that might show a good treatment response – and this is beneficial to both patients and doctor. The importance of biomarkers is reflected by the fact that currently more than half of Phase 1 studies have PD as an objective (see Figure 3).

Figure 3: Objectives



Trial Summary

Based on the analysis of recently published Phase 1 studies in oncology, it can be concluded that a typical Phase 1 study nowadays has the following characteristics:

- The Phase 1 trial will be a pharma-sponsored study, enrolling 15-44 patients at 1-3 sites in the US, Japan or Western Europe
- The drug will be given either PO or IV and five dose levels will be tested
- The enrolment will take between 17-33 months, and patients with indications such as colorectal, prostate, liver, breast and lung cancer and melanoma are most likely to be enrolled
- The objectives of the study will include safety, tolerability, efficacy, PK and PD

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3. Reference list of 191 Phase 1 articles. Visit: www.sms-oncology.com/news/downloads

About the authors

Lindy Bosch is Business Developer at SMS-oncology, where she is responsible for acquiring new and maintaining existing relationships with clients. She recently obtained her MSc in Biomedical Sciences from the University of Groningen, The Netherlands, having focused her Bachelor's and Master's research projects on oncology. Lindy also has a strong commercial passion and studied science, business and policy as part of her Master's course. Email: l.bosch@sms-oncology.com

Raymond Hoffmans is Chief Business Development Officer at SMS-oncology, where he is responsible for acquisition and new business opportunities. He joined the company in 2010 as a consultant, and has been involved in many consulting and medical writing projects. Raymond received his MSc in Biology from the University of Utrecht and his PhD from the University of Zurich. He performed his postdoctoral fellowship at the Dana Farber Cancer Institute, Boston, and at the Hubrecht Institute, Utrecht, where he focused on the molecular mechanisms of signaling pathways in cancer. Email: r.hoffmans@sms-oncology.com